is remembered that all applications of the aconitines, externally, are to be considered dangerous if any abrasion of the skin is present.

The chemical part of this inquiry has been conducted in the Laboratories of the Scientific Department of the Imperial Institute, with the assistance and co-operation of the Government of India. Our thanks are specially due to Dr. George Watt, C.I.E., Reporter on Economic Products to the Government of India, for the interest he has shown in the investigation, and for the care he has taken in the collection of the necessary material.

The physiological experiments have been conducted in the Department of Materia Medica and Pharmacology of the University of Aberdeen, and have been assisted by a grant made by the Royal Society from the Government Fund. The assistance of Drs. Esslemont and Fraser has been very valuable in carrying out some of the observations entailed in this department of the research.

"The Pharmacology of Pyraconitine and Methylbenzaconine considered in Relation to their Chemical Constitution." By J. Theodore Cash, M.D., F.R.S., Regius Professor of Materia Medica in the University of Aberdeen, and Wyndham R. Dunstan, M.A., F.R.S., Director of the Scientific Department of the Imperial Institute. Received June 11,—Read June 20, 1901.

(Abstract.)

In a previous paper* we have shown that an entire change in the physiological action ensues on the withdrawal of the acetyl group from aconitine as is seen in the action of benzaconine, the first hydrolytic product of aconitine, from which it differs in containing an atom of hydrogen in the place of one acetyl group. This alkaloid is devoid of the characteristic physiological action and extraordinary toxicity of aconitine, whilst in respect of its action on the heart it is in the main antagonistic to that of the parent alkaloid. In order to study further the remarkable dependence of the physiological action on the presence of the acetyl group, we have examined the action of two derivatives of aconitine which we have obtained in this research, viz., pyraconitine and methylbenzaconine.

Pyraconitine was first prepared by one of us† by heating aconitine at its melting point, when the acetyl group is expelled as one molecule of acetic acid and the alkaloid pyraconitine remains. This compound

* 'Phil. Trans.,' B, 1898, vol. 190, p. 239.

† Dunstan and Carr, 'Trans. Chem. Soc.,' 1894, vol. 65, p. 176.

therefore differs in composition from aconitine by the loss of one molecule of acetic acid, and from benzaconine by one molecule of water.

Methylbenzaconine was obtained from aconitine by heating it with methyl alcohol in a closed tube.* A remarkable reaction takes place, in which the acetyl group is ejected as acetic acid, a methyl group taking its place. This alkaloid therefore differs from aconitine in containing a methyl group in the place of the acetyl group, and from benzaconine in containing a methyl group in the place of one atom of hydrogen. The examination of its physiological action would therefore be the means of studying the result of replacing in aconitine the negative radical acetyl by the positive methyl group, and also of studying the effect of the introduction of methyl in modifying the physiological action of benzaconine.

The acetyl group of aconitine evidently occupies an exceptional position in the molecule of aconitine. So far as we are aware it is the only acetyl compound at present known, which exchanges this group for methyl when it is heated with methyl alcohol. We have examined the behaviour of numbers of different types of acetyl derivatives from this point of view and can find none analogous to aconitine.

For the study of their physiological action these alkaloids have been specially purified and employed as hydrobromides in aqueous solution.

Contrasting the physiological action of pyraconitine with that of aconitine, as described in the present paper, we find, as might be anticipated from our previous results, that through the removal of the acetyl group the great toxicity of aconitine is nearly entirely abolished and the characteristic features of aconitine poisoning are no longer produced by pyraconitine.

Contrasting the physiological actions of benzaconine and pyr aconitine which differ from each other empirically by one molecule of water, pyraconitine, the anhydride, is the more active compound. Both these alkaloids, divested of the acetyl group of aconitine, are relatively weak and feebly toxic when compared with the parent alkaloid.

Although benzaconine and pyraconine exhibit a strong similarity in the physiological effects they produce, there are differences between them which are probably more considerable than they would be if pyraconitine were merely the anhydride of benzaconine.

The substitution in aconitine of methyl for acetyl which occurs in the formation of methyl benzaconine has led to a very considerable reduction in toxicity and has introduced a curare-like effect similar to that first observed by Crum Brown and Fraser† to result from the

* 'Proc. Chem. Soc.,' 1896, p. 159.

† 'Trans. Roy. Soc. Edinb.,' 1869, vol. 25, p. 192.

introducton of methyl into the molecule of an alkaloid. Methyl benzaconine is however more toxic and generally more powerful than benzaconine, owing to the presence of the methyl group.

Action of Pyraconitine.

The main effects of pyraconitine may be thus summarised. Its local application is devoid of the effects characteristic of the aconitines. Its chief action upon the heart is to cause slowing, partly from vagus irritation, partly from depression in function of intrinsic rhythmical and motor mechanisms.

There is less tendency to want of sequence in the cardiac chamber walls than is observed after the aconitines and benzaconine.

The vagus apparatus remains active in degree after doses somewhat in excess of the lethal, the slowed heart of pyraconitine being accelerated both by vagotomy and by atropine.

Activity of respiration is reduced (by central depression) to a degree incompatible with life, as is the case after aconitine and benzaconine. The peripheral motor nerves and muscular tissues are not at this time markedly affected. Artificial respiration prolongs life, but the slowed heart and greatly reduced blood pressure tend to a fatal issue.

The spinal cord is impaired in its reflex function, apparently secondarily to reduced circulation in its structure. A tendency to tonic spasm in frogs is late in appearing and of moderate degree. It has not been seen after destruction of brain and medulla. It is further associated with a curious condition of exaggerated motility.

Neither muscular nor intramuscular nervous tissue are strongly influenced by pyraconitine in lethal or somewhat hyperlethal doses. The lethal dose per kilo. frog's weight is practically about twelve times that which is lethal per kilo. rabbit's weight.

Contrasted Effects of Pyraconitine and Benzaconine.

Of these two alkaloids, pyraconitine is approximately six to seven times more toxic towards mammals (rabbits and guinea-pigs) than benzaconine, and five to six times more so towards frogs. They are alike in their action upon mammals, in so far as they are non-irritant, that they slow the respiration without preliminary acceleration, that they slow the heart and reduce the blood pressure to a very low level, that they cause paresis and in guinea-pigs clonic movements, and that respiratory failure is the immediate cause of death. They differ in so far that pyraconitine acts more rapidly, but for a shorter period, whilst fatal termination of poisoning is preceded by convulsions, which are very rare after benzaconine. Benzaconine alters the sequence of the ventricles upon the auricles much more usually and

to a greater extent than pyraconitine, though if asequence is developed it has the same general character (the auricular second beat being blocked from the ventricle).

Whilst pyraconitine stimulates the cardiac vagus both centrally and within the heart (section and atropine causing acceleration), and finally occasions only a limited reduction in its activity, benzaconine produces but little stimulation, and ultimately suspends the vagus inhibitory action. Under these conditions atropine is, of course, inoperative. Both accelerate the heart in small, but slow it in large, dose, and both may disorder the sequence, but vagus inhibition is much more interfered with by benzaconine. Frogs poisoned by benzaconine lose the power of voluntary movement, then reflex disappears, and finally the circulation is arrested; but after pyraconitine, reflex outlasts the heart's action. Late spasm occurs after the latter, not after the former. Whilst in lethal doses pyraconitine has no effect beyond somewhat favouring fatigue and reducing excitability of motor nerves, benzaconine greatly impairs their function, and in thorough poisoning may suspend it entirely.

Action of Methylbenzaconine.

The action of methylbenzaconine may be summed up as follows: It is very feeble in its toxicity when contrasted with aconitine, but is somewhat stronger than benzaconine.

Small and medium doses, whilst slowing the heart, do not cause any failure in sequence, but larger doses have this effect. They act upon the rhythm of the organ, involving the movement of the auricle and ventricle whilst ultimately the sequence of the latter upon the former is impaired, so that it follows only a certain proportion of the auricular "leads." This block is not removed by atropine. Whilst the passage of the ventricle into the diastole is at first retarded, the contractile power of the myocardium is ultimately reduced by methylbenzaconine.

The cardiac vagus is depressed in action and its inhibitory function is ultimately suspended by large doses, neither section of the vagus nor atropine administration relieving the slow and faulty action of the organ.

There is evidence of slight primary stimulation of reflex cord centres when ligature of vessels prevents the masking of this condition by the peripheral action of the poison. The subsequent impairment in cord reflexes is later in occurring and of much shorter duration than the action of methylbenzaconine upon intramuscular motor nerves.

In mammals the paralytic symptoms are predominant, the fall of temperature is in part attributable to this cause as well as to changes in the circulation. The clonic movement and salivation (observed in

a certain stage of the action of methylbenzaconine, especially upon guinea-pigs) are suggestive of the action of a near ally of aconitine. In frogs, however, there is no semblance to an aconitine effect, unless its very feeble action towards sensory nerves or its much more powerful action upon motor nerves, be thus viewed. Motor nerves are greatly affected by doses which are distinctly below the lethal for cold-blooded animals, the action being curare-like in character. Muscular tissue is after the action of large doses more susceptible of fatiguing influences. Fibrillation in muscles to which the poison has access is more common than after aconitine or any other derivative examined.

These observations support in the main the contention of Crum Brown with Fraser that the introduction of methyl into the molecule of certain spasm-producing alkaloids, marks the effect of these by occasioning a curare-like action at the periphery.

Contrasted Effects of Methylbenzaconine and Aconitine.

The toxicity of aconitine is, roughly, eighty to one hundred times that of methylbenzaconine towards rabbits and guinea-pigs, and much the same proportion holds for summer and winter frogs respectively. Whilst slight tendency to salivation and retching movements are produced by methylbenzaconine, and are in so far suggestive of a slight aconitine action, the absence of initial acceleration of respiration, of local irritation, and dyspnœal convulsions, and the predominance of paralytic symptoms, are points of difference. The action upon the heart is entirely distinct, for the pulse is slowed by methylbenzaconine, the auricles eventually beating more rapidly than the ventricles, the action of the poison proceeds uniformly and without the intermissions which characterises aconitine, whilst the early phenomena of vagus stimulation have little in common. The general symptoms of poisoning in frogs have scarcely a point of similarity, quiescence, rapid failure of reflex, and voluntary movement, without impairment of the cardiac action, are distinctive of methylbenzaconine, whilst excitement with great motility and persistence of voluntary movement follow aconitine. Fibrillation is much more pronounced after the former, though it is only a transitory phenomenon. The action on the heart differs widely in frogs as it does in mammals, whilst the curare-like action of the derivative on motor nerves is not produced by aconitine in doses which just suffice to arrest the heart.

It is true that large but sublethal doses of aconitine are followed by a condition of almost complete paralysis, which lasts for several days, but during this time there is slight voluntary and reflex movement, the nerve-endings are not put out of action, and the circulation is usually of the feeblest character, all conditions which are not found in the period of quiescence following methylbenzaconine.

Contrasted Effects of Methylbenzaconine and Benzaconine.

Methylbenzaconine is from three to four times more toxic towards rabbits and guinea-pigs than benzaconine, and from twice to thrice as toxic towards frogs (*R. temp.* and *R. esc.*). In mammals, slight salivation, retching movements, and muscular tremor are characteristic effects of the former, but dyspnœa, ataxia, and paresis are also seen after benzaconine. Of the two, methylbenzaconine is distinctly less depressant towards the heart. Slowing of the pulse and want of sequence of ventricular upon auricular action occurs after both, but is a much earlier symptom after benzaconine, which causes more disorder in the motor mechanism. On the other hand, the intracardiac vagus is put out of function more readily by methylbenzaconine. Death after either poison is rarely preceded by spasm. Neither of the two compounds cause any local irritation in frogs, but methylbenzaconine produces active fibrillation in the muscles, to which it gains access and develops a complete curare-like action much more prominently than does benzaconine, the heart continuing to beat strongly. Benzaconine, in dose sufficient to cause such an effect at the periphery, acts disastrously upon the circulation. In partial poisoning by methylbenzaconine the characteristic rapid failure of the intramuscular motor nerves on stimulation is well marked, but the subsequent recovery on resting, so characteristic of benzaconine, has not been observed.

"On the Separation of the Least Volatile Gases of Atmospheric Air, and their Spectra." By G. D. Liveing, M.A., Sc.D., F.R.S., Professor of Chemistry in the University of Cambridge, and James Dewar, M.A., LL.D., F.R.S., Jacksonian Professor in the University of Cambridge, Fullerian Professor of Chemistry, Royal Institution, London. Received June 15,—Read June 20, 1901.

Our last communication to the Society* related to the most volatile of the atmospheric gases, that which we now beg leave to offer relates to the least volatile of those gases. The former were obtained from their solution in liquid air by fractional distillation at low pressure, and separation of the condensible part of the distillate by cooling it in liquid hydrogen. The latter were, in the first instance, obtained from the residue of liquid air, after the distillation of the first fraction, by allowing it to evaporate gradually at a temperature rising only very slowly. The diagram, fig. 1, will make the former process intelligible.

* 'Roy. Soc. Proc.,' vol. 67, p. 467.